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Update: Development of White Papers and Standard Scripts for Analysis and Programming

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ABSTRACT

A PhUSE Computational Science (CS) Working Group is creating white papers describing recommended analysis and reporting methods for frequently-collected types of data included in clinical trials and regulatory submissions. An online platform for sharing code has also been created, making these standards easy to implement. This paper provides an update as of April 2015 on the progress made in these efforts.

INTRODUCTION

Industry standards have evolved over time for data collection (CDASH), observed data (SDTM), and analysis datasets (ADaM). Creating a consistent set of analyses and reports, at least for safety, is the natural next step in this remarkable journey. Members of a PhUSE CS Working Group are creating white papers outlining recommendations for safety analysis and reporting for clinical trial study reports and integrated safety-related submission documents. Development of standard tables and figures with associated analyses will lead to improved product life-cycle evaluation by ensuring reviewers receive optimal analyses for the evaluation of patient safety. More importantly, having an organized process for shared learning of improved methodologies can lead to earlier safety signal detection and better characterization of the safety profile of the products. Additionally, a platform for sharing code to implement the recommendations has been created and is ready, making the standards easy to use. Crowd sourcing for code development will enable consistent interpretation of methods and substantial savings in resourcing across the industry. In addition, these code modules will be validated, with corresponding documentation, for easier adoption by industry. This paper describes the progress on these efforts and how people can participate in the creation and use of cross-industry analysis and reporting standards.

WORKING GROUP DESCRIPTION

The goal of the Working Group is to produce recommendations and establish a platform for the collaborative development of specialized programs to be used as analytical tools for clinical trial research, reporting, and analysis. This platform includes:

- Identification of areas that can benefit from a standard set of analyses
- Development of recommendations for analyses, tables and figures within a topic area
- Creation of a process and guidelines for documentation and management of scripts
- Incorporation of data standards whenever feasible

The Working Group is led by a team of representatives from both industry and the FDA. Mary Nilsson is the industry co-lead, with Hanming Tu as the project manager; Steve Wilson and Mat Soukup are the current FDA liaisons. There are two main areas of focus - the creation of white papers outlining recommendations for analysis and reporting of different types of safety data, and the development and qualification of scripts (programs) for generating the data displays shown in the white papers.

WHITE PAPERS

The following white papers have been drafted, or are in progress (more current information on their status will be presented at the conference, as work is still ongoing):

1. Analyses and Displays Associated with Measures of Central Tendency – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Summary Documents *(finalized in October 2013, scripts developed for displays at the March 2014 Computational Science Symposium and October 2014 PhUSE conferences, Version 2 expected by March 2016 to include ADaM specifications)*

2. Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal – With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Summary Documents *(final white paper expected by June 2015)*
3. Analyses and Displays Associated with Adverse Events – With a Focus on Phase 2-4 Clinical Trials and Integrated Summary Documents *(second draft for public comment expected by June 2015; final white paper expected by March 2016)*
4. Analyses and Displays Associated with Demographics, Disposition, and Medications – With a Focus on Phase 2-4 Clinical Trials and Integrated Summary Documents *(finalized in September 2014, scripts developed for displays at the October 2014 PhUSE conference)*
5. Analyses and Displays Associated with Hepatotoxicity – With a Focus on Phase 2-4 Clinical Trials and Integrated Summary Documents *(1st draft for public comment expected by June 2015; final white paper expected by March 2016)*
6. Analyses and Displays Associated with Non-Compartmental Pharmacokinetics – With a Focus on Clinical Trials *(finalized in March 2014)*
7. Analyses and Displays Associated with QT Studies *(1st draft for public comment expected by June 2015; final white paper expected by March 2016)*
8. Analyses and Displays Associated with Questionnaire Data *(joint effort with ADaM ADQS sub-team, targeting initial draft for Summer 2015)*
9. Analyses and Displays Associated with Events of Special Interest *(new white paper, recruiting people to help)*

The scope of the white papers includes information that would normally be included in a Statistical Analysis Plan, plus any associated table, listing and figure shells, and detailed information that might be required for performing the analysis, including examples of analysis datasets and related metadata. However, actual implementation details, such as page layouts and margin requirements will not be addressed. Recommendations for difficult or potentially controversial decisions related to analyses or displays will be provided where possible; when a decision cannot be reached, a description of the issues that have been considered will be included.

Our goal is to have additional white papers completed and available for public download from the publications section of the PhUSE website (http://www.phuse.eu/publications.aspx). Drafts can be viewed in the CS Working Groups section of the PhUSE Wiki (http://www.phusewiki.org/wiki/index.php?title=WG5_Project_08). These white papers will also be presented at several industry conferences during the upcoming year.

SCRIPT REPOSITORY

The script repository project has established the basic structure and management of the GitHub repository to be used for development and storage of the PhUSE standard scripts, which have recently been moved from Google Code. GitHub provides a scalable, reliable, and fast collaborative development environment for developing and sharing standard scripts and documents for data transformations and analyses. The goals of this project are to:

- define the folder structure and name conventions
- define roles and responsibilities for each role
- define tasks and duties
- define the process of tracking issues
- define required metadata and recommended programming style for scripts
- provide test data and validation documentation

The script repository is intended to be language-independent, but with a primary focus on SAS and R, as those are currently the two main languages used for reporting and analysis within the industry.

Some scripts have already been developed; a complete index is available on the PhUSE Wiki, at http://www.phusewiki.org/wiki/index.php?title=Standard_Script_Inventory. The MIT license governing the development and distribution of open source code was chosen, in order to make all scripts freely available for use. The PhUSE script repository can be accessed at http://code.phuse.com, and instructions for using the new GitHub repository will be developed soon.

Scriptathons were held at the 2014 PhUSE CSS, PharmaSUG and PhUSE conferences, with the resulting scripts stored in the Source section of the repository. Approximately 30 scripts are currently stored. Scripts developed at

the 2014 conferences used data sets from the updated CDISC ADaM pilot as input, and produce output as described in the published white papers.

The next step is to determine how to review, test and qualify scripts that are stored in the repository for general use. Efforts began at the 2015 PhUSE CSS conference to develop a process for qualifying the scripts for use, and then begin the actual qualification steps. The scripts developed for the Measures of Central Tendencies white paper will serve to test and refine the proposed qualification process. Please see PharmaSUG 2015 Paper AD10, "Qualification Process for Standard Scripts in the Open Source Repository with Cloud Services" for more information about the qualification process itself. The PhUSE Wiki page for Project 02 (Repository Content and Delivery, http://www.phusewiki.org/wiki/index.php?title=WG5_Project_02) also contains related links and details on the current status of the project.

We are encouraging people to submit additional scripts, along with their ideas for others that should be written, with a goal of building a repository that people can borrow from for their own projects. In addition, we are actively recruiting help with the process of qualifying existing scripts for public use.

CONCLUSION

This paper is intended to serve as an update as of April 2015 on the progress made by the Standard Scripts Working Group in developing white papers outlining recommendations for analysis and reporting of various types of clinical trial safety data, and the creation of scripts for generating the data displays described in the white papers. As part of this effort, a GitHub repository has been created, and the Working Group is actively seeking contributions to the code library. If you would like to get involved in these efforts, please see the PhUSE Wiki for instructions on contacting the Working Group leadership team.

REFERENCES

Standard Scripts Project 1 (Discovery / Acquisition)- http://www.phusewiki.org/wiki/index.php?title=WG5_Project_01

Standard Scripts Project 2 (Repository Content / Delivery)-
http://www.phusewiki.org/wiki/index.php?title=WG5_Project_02

Standard Scripts Project 3 (Repository Governance / Infrastructure)-
http://www.phusewiki.org/wiki/index.php?title=WG5_Project_03

Standard Scripts Project 8 (White Papers)- http://www.phusewiki.org/wiki/index.php?title=WG5_Project_08

DiTommasi, Dante; Hurley, Christopher; Spruck, Dirk; Tu, Hanming. 2015. "Qualification Process for Standard Scripts in the Open Source Repository with Cloud Services." PharmaSUG 2015 Conference Proceedings.

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